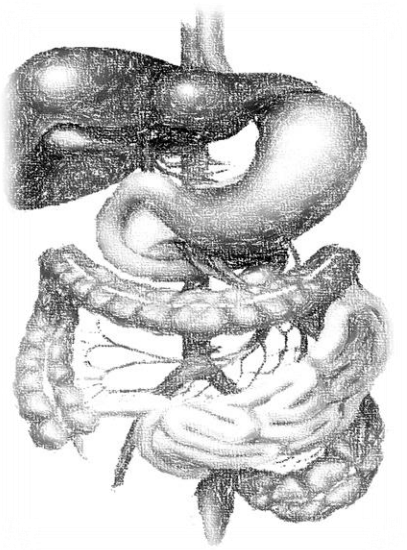
MEDICINE
KING SAUD UNIVERSITY

436 team
pharmacology

تمت المراجعة
شوق الأحمري & عبدالعزيز العنقري



10: Anti-malarial drugs

objectives

- Classify the main antimalarial drugs depending on their goal of therapy
- Detail the pharmacokinetics & dynamics of main drugs used to treat attack or prevent relapses
- State the WHO therapeutic strategy for treatment
- Hint on the CDC recommendations for prophylaxis in travelers to endemic areas

Color index

- extra information and further explanation
- important
- doctors notes
- Drugs names
- Mnemonics

We highly recommend you to study Microbiology lecture “Malaria” before studying this lecture

Kindly check the editing file before studying this document

تم بحمد الله

كل الشكر لـ(أعضاء فريق علم الأدوية) المتميزين
اشتغلوا في أكثر بلوك مضغوط في كل سنوات العلوم الأساسية وما قصروا أبد

لا تنسوهم من دعواتكم ♥

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قادة فريق علم الأدوية :

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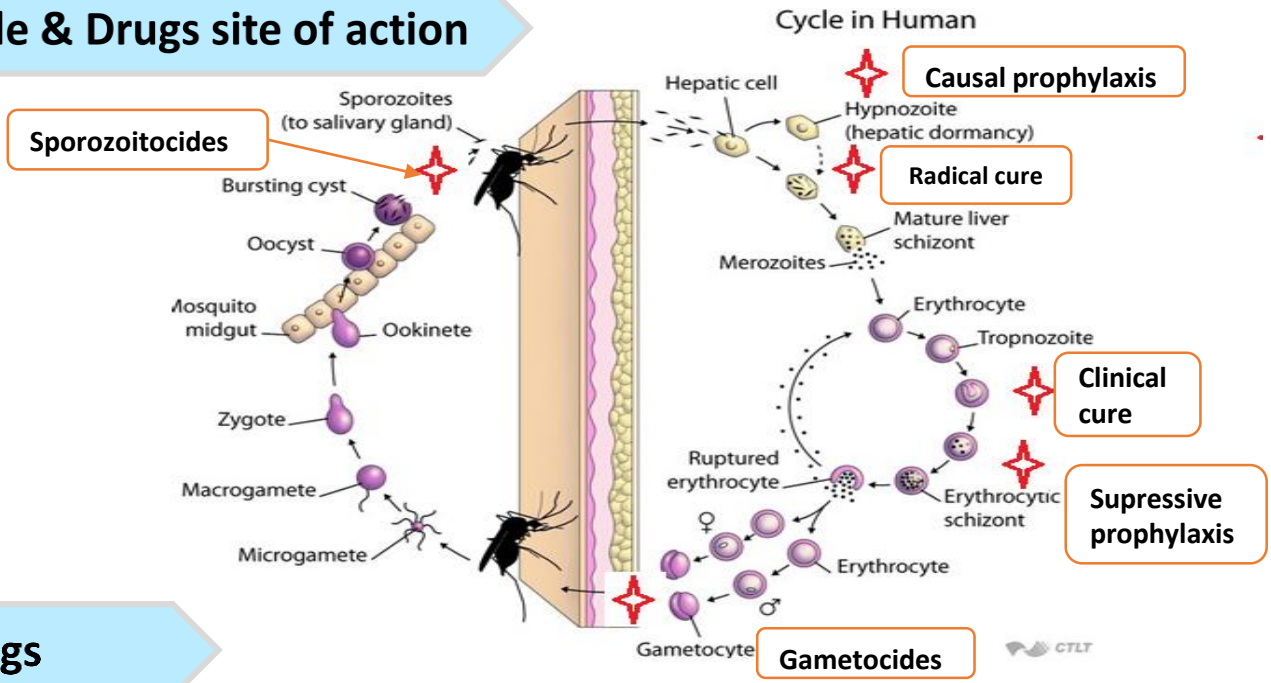
- فارس النفيسة

Overview

Cycle & Drugs site of action



Drugs

Antimalarial By Armando (15:55 min) amazing video!

Antimalarial By Efham (19:15 min) amazing video!

Antimalarial drugs

- **Causal prophylaxis** → Destroys parasite in liver cells & prevent invasion of erythrocytes → Primaquine
  - The **primary** site of infection is **liver**
- **Suppressive prophylaxis** → Suppresses the erythrocytic phase & thus attack of malaria fever → Chloroquine, Mefloquine, Doxycycline
- **Clinical cure** (erythrocytic schizonicide) Used to terminate an episode of malarial fever
  - Fast acting high efficacy → Chloroquine, Quinine, Mefloquine, Artemisinin
  - Slow acting low efficacy → Pyrimethamine, Proguanil, Sulfonamides
    - ميثاء مين ؟ اللي بروقان تسولف ؟
- **Radical cure** → Eradicate all forms of vivax from the body → Suppressive drug + Hypnozoitocidal
- **Gametocidal** → Destroys gametocytes & prevent transmission
  - Against vivax: Chloroquine, Quinine
  - Against all species : Primaquine
- **Sprozoitocides** → Destroys sporozoites → Proguanil, Pyrimethamine

Antimalarial drugs

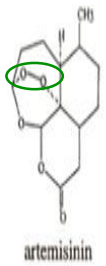
Drug

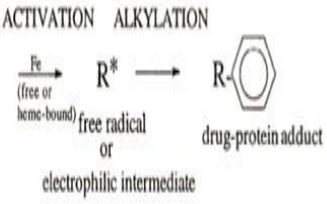
Artemesinin most potent

Action/Mech. of action

They have **endoperoxide bridges** that are cleaved by haem iron **to yield carbon- centered free radicals**, that will:

- Alkylate membranes of parasite's food vacuole and mitochondria → no energy
- **Irreversibly bind & inhibit sarco-endoplasmic reticulum Ca^{2+}-ATPase of the parasite**, thereby inhibiting its growth
- Inhibiting formation of transport vesicles → no food vacuoles





Pharmacodynamics

- Artemisinin is the active principle of the plant *Artemisia annua* **(qinghaosu)**
- Fast acting blood **Schizontocide**
- **Affect all forms** including multi-drug resistant *P. falciparum*
- Short duration of action (Artemisinin = diminishing)
- High recrudescence rate (after short-course therapy Female only)
- Poorly soluble in water & oil, can only be used orally
- Artemisinin & its analogs are very rapidly acting blood schizonticides against all human malaria parasites. **No effect on hepatic stages.**

The drug has a unique structure (endoperoxide bridges), it will bind with the iron of the patient to help the drug to release free radicals → destroy multiple things in the parasites and eventually kill them

Pharmacokinetics

- Rapidly bio transformed in liver into dihydroartesiminin → active metabolite
- Artemisinin ,Artesunate, Artemether are prodrugs
- Derivatives (^) are rapidly absorbed orally
- Widely distributed
- t½ Artemisinin: 4hrs / Artesunate: 45min / Artemether: 4-11hrs
- Artesunate (water-soluble; oral, IV, IM, rectal administration)
- Artemether (lipid-soluble; oral, IM, and rectal administration)
- Dihydroartemisinin (water-soluble; oral administration)
- Induce its own CYP-mediated metabolism→ ↑ clearance 5 fold so its efficacy will decrease (this is a disadvantage of Artemether)

Clinical uses

Because Artemisinin derivatives have short t ½ :

1. Monotherapy should be extended beyond disappearance of parasite to prevent recrudescence
1. By combining the drug with long- acting antimalarial drug ex:(Mefloquine Female only) only we need to know its name & that it is long- acting antimalarial drug

ADRs

- Transient heart block
- Decrease neutrophil count
- Brief episodes of fever because of its effect on the RBCs, which indicate high dose
- Resistance → was reported recently in Cambodia- Thailand border

Preparation

I love sun and eating (ate)

- Artesunate IV or IM preparations for severe complicated cases as cerebral malaria (24h) followed by complete course of ACT
- **A**rtemisin-based **C**ombination **T**herapies (ACTs):given as a tablet
  - Artemether + lumefantrine
  - Artemether + amodiaquine
  - Artemether + mefloquine
  - Artemether + sulfadoxine - pyrimethamine

Antimalarial drugs

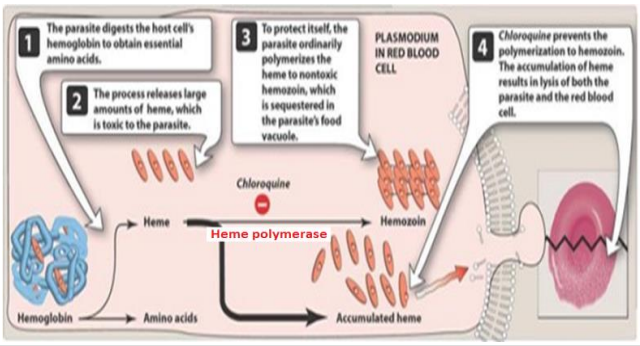
Drug

Chloroquine very famous, effective, safe & very old drug

Mechanism of action

- Malaria Parasite digest host cell's Hb to obtain amino acids (remember: if we breakdown Hb → amino acids)
- Heme is released → Toxic to the parasite
- So parasite detoxifies it (by **heme polymerase** (an enzyme inside the parasites) →to Hemozoin (Nontoxic) & traps it in food vacuole

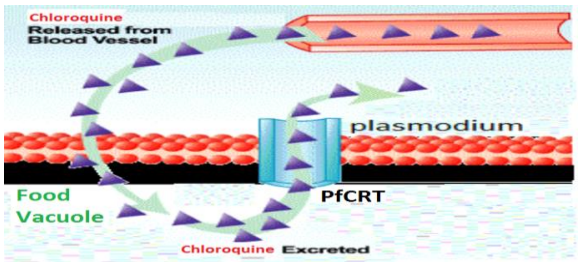
Chloroquine block This enzyme, so heme stays and kills the parasite, because heme is toxin for the parasite



Resistance

- Resistance (it's a disadvantage in all antimalarial drugs) against the drug develops as a result of mutation of the chloroquine resistance transporter (PfCRT)
- PfCRT enhances the efflux of chloroquine from the food vacuole

الدواء يدخل للبارسايت من الدم عن طريق الفود فاكيول ومع الوقت يصير طفرة في الباراسيت فيطور ناقل على سطحه يطلع الكلوروكوين منه فما يقدر يأثر عليه الدكتور نبه كثير إن هذا الدوا صار عنده مقاومه



P.D

- Safe in pregnancy نقول للحامل " كولي يا الملكة" ما راح يجيك شيء إن شاء الله
- Potent blood **Schizontocide**
- Active against all forms of the schizonts (exception is chloroquine-resistant P.f. *" P. falciparum"* & P.v. "P. **vivax**")
- No activity against tissue shizonts. blood only
- Gametoside: Against all species **except *P. falciparum***
- It has antipyretic effect, and it is cheap

Pharmacokinetics

- Rapidly & completely absorbed from the GIT PO=orally
- Has high volume of distribution(100-1000 L/kg)
- Concentrated into parasitized RBCs
- Released slowly from tissues
- Metabolized in the liver
- Excreted in the urine 70% unchanged
- Initial t½ =2-3days & terminal t ½=1-2months has 2 compartmental diffusion

1- First it will go to highly perfusion tissues e.g.: liver, heart lung
2- After 2 or 3 days it will go to low perfusion tissues e.g.: bone

Uses

- Used **to eradicate blood schizonts of *Plasmodium.*** (It is given in loading dose to rapidly achieve effective plasma conc. Female only)
- Hepatic amoebiasis
- Rheumatoid arthritis

ADRs

Therapeutic dose:

- Mild headache and visual disturbances
- Gastro-intestinal upsets; Nausea, vomiting
- Pruritus, urticaria.

Prolonged therapy (more than 3 days) or in high dose**:**

- Ocular toxicity: Loss of accommodation, lenticular opacity (cataract), retinopathy فلازم نتاكد ان المريض ما يكون عمره كبير
- Ototoxicity
- Weight loss
- Bolus injection → hypotension & dysrhythmias

Antimalarial drugs

Drug	Quinine
M.O.A	Same as chloroquine
Resistance	Like chloroquine by mutation of chloroquine resistance transporter (PfCRT), also increased expression of P-glycoprotein transporter (the parasite will increase the transporter to get ride of Quinine. So it has double resistance)
Pharmacokinetics	▪ Rapidly & completely absorbed from the GIT ▪ Peaks after 1-3 hours ▪ Metabolized in the liver & excreted in urine ▪ 5-20% excreted in the urine unchanged ▪ t½ = 10 hours but longer in sever falciparum infection(18hrs) ▪ Administered: orally in a 7 day course or by slow IV for severe *P. falciparum* infection
Pharmacodynamics	▪ Safe in pregnancy الحامل كالملكة ▪ The main alkaloid in cinchona bark ▪ Potent blood Schizontocide of all malarial parasites & weak gametoside for vivax & ovale (but not falciparum. It is Not active against liver stage parasites (Female only) ▪ Depresses the myocardium, reduce excitability & conductivity ▪ Mild analgesic, antipyretic, stimulation of uterine smooth muscle, curare mimetic effect (muscle relaxant)
Uses	▪ Parenteral treatment of severe falciparum malaria ▪ Oral treatment of falciparum malaria ▪ Nocturnal leg cramps Nocturnal leg cramps = involuntary contraction of the muscle ▪ The drug effective in some patient and not effective in other patients

Quinine (con.)

Drug	Quinine
ADRs	With therapeutic dose: poor compliance → bitter taste. some patients stop the drug because of its bad taste (this taste comes from the planet) Higher doses: ملكة البحر المتوسط - Blood dyscrasias; anemia, thrombocytopenic purpura & hypoprothrombinemia. - Blackwater fever (RBCs will rapture and appear in urine, which will give the urine dark color), a fatal condition in which acute hemolytic anemia is associated with renal failure (due to hypersensitivity reaction to the drug Female only) - Cinchonism: (tinnitus, deafness, headaches, nausea & visual disturbances) - Abdominal pain & diarrhea - Hypotension & arrhythmias, hypoglycemia, because the drug enhance the secrestion of insulin (only if we give it as IV) - Rashes, fever, hypersensitivity reactions - If given IV → neurotoxicity → tremor of the lips and limbs, delirium, fits (نوبة), stimulation followed by depression of respiration & coma
Contraindications	الملكة موب طويلة بال أبداً - Prolonged QT Interval type of arrhythmia - Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency - Myasthenia Gravis, the drug cause muscle relaxant and in Myasthenia Gravis most of the muscle relax (because the muscles lost their receptors for Ach → no AP → no contraction) - Hypersensitivity - Optic Neuritis, auditory problems - Dose should be reduced in renal insufficiency because the drug secreted by kidney
Drug interactions	- Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of Quinine, antacids bind with Quinine and decrease its absorption - Mefloquine, because it cause prolonged QT interval - Quinine can raise plasma levels of warfarin and digoxin

Antimalarial drugs

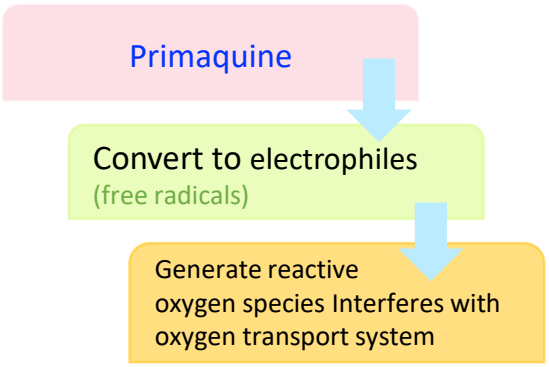
Drug

Primaquine

Action/Mech. of action

Not well understood. It may be acting by:-

- Generating ROS → can damage lipids, proteins & nucleic acids of the parasite
- Interfering with the electron transport in the parasite → no energy
- Inhibiting formation of transport vesicles → no food vacuoles
- Resistance: Rare when Primaquine & Chloroquine are combined



P.D

- Hypnozoitocides → against liver hypnozoites & gametocytocides (the only drug can act on the liver)
  The **primary** site of infection is **liver**
- Against the 4 human malaria species Female only
- Radical cure of *P. ovale & P. vivax*
- Prevent spread of all forms (chemoprophylaxis) so it can be given as a prophylactic

P.K

- Well absorbed orally
- Rapidly metabolized to etaquine & tafenoquine → more active (t½ → 3-6h)

Indications

- Radical cure of relapsing malaria, 15mg/day for 14 days
- In falciparum malaria: a high single dose (45mg) to kill gametes & cut down transmission
- G-6-PD normal → 15 mg\day for 14 days
- G-6-PD deficiency (mild African form) → 45 mg\week for 8 weeks
- G-6-PD deficiency (more sever mediterranean variety) → 30 mg\week for 30 weeks

The three doses are very important

ADRs

At regular doses

- patients with G-6-PD deficiency → hemolytic anemia. Because the free radicals will rapture the RBCs
- Oxidation of Primaqune produces free radicals, free radicals will cause oxidative damage of RBCs → Hemolysis

At larger doses:

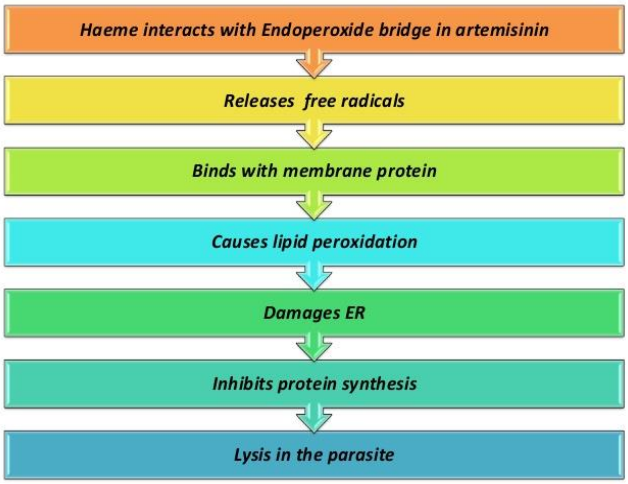
- Epigastric distress & abdominal cramps
- Mild anemia, cyanosis (bluish discoloration of nails and limbs) & methemoglobinemia
- Severe methemoglobinemia → rarely in patients with deficiency of NADH methemoglobin reductase.
- Granulocytopenia & agranulocytosis (rare) reduction in granulocyte

Contraindications

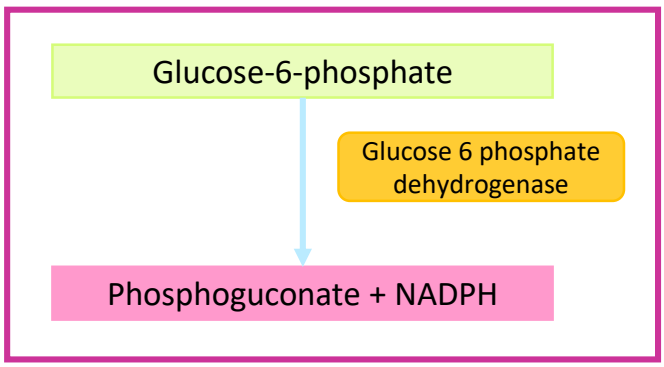
- Should be avoided in pregnancy (the fetus is relatively G6PD-deficient and thus at risk of hemolysis)
- G6PD deficiency patients

To understand !

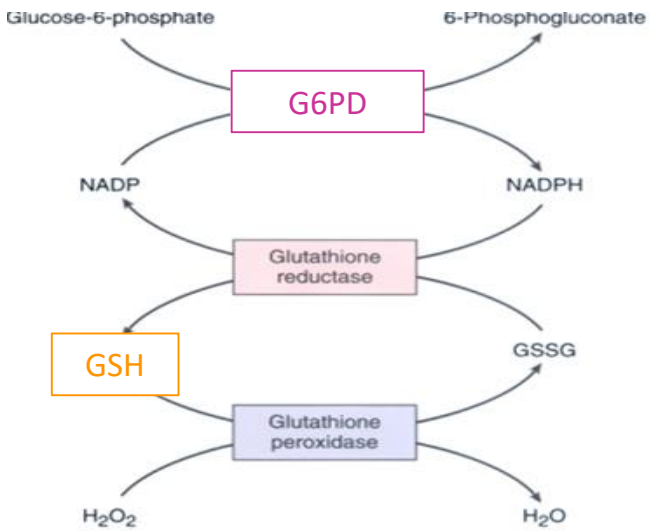
الصور موجودة في سلايدز الدكاترة لكن الشرح إضافة من عندنا



Mechanism of action for Artemesinin

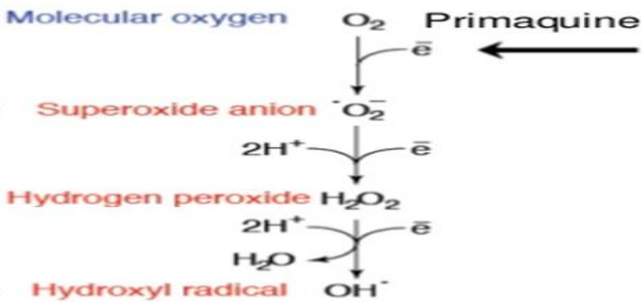


- This reaction happen inside the RBCs, the G-6-P will be converted into phosphoguconate and NADPH via Glucose 6 phosphate dehydrogenase (G-6-P-D)
- The NADPH will go to the glutathione system (antioxidant system)
- Any decrease or deficiency in (G-6-P-D) will decrease the production of NADPH, so decrease the efficient of glutathione system



أحد antioxidant systems هو glutathione اللي يحول H_2O_2 إلى H_2O، كيف؟ فيه عندنا انزيم اسمه glutathione peroxidase راح يشيل ذرة الأوكسجين الموجودة في H_2O_2، لكن يحتاج مادة عشان تخليه active وهم بعد عشان ينقل لها هذا الأوكسجين، من هالمادة؟ GSH، لمن يشتغل الأنزيم ويسوي شغله راح يتحول GSH إلى GSSG. نحتاج نحوله مره ثانية إلى GSH عشان نستفيد منه مره ثانية، كيف؟ عن طريق NADPH
لو افترضنا ما صار عندنا NADPH وش راح يصير؟ ما نقدر نرجع GSH بالتالي ما راح نحفز الأنزيم بالتالي ما نقدر نتخلص من H_2O_2. وهذي المادة تعد ROS وتقدر تدمر أشياء كثيرة من ضمنها RBCs

أخذناها في الكارديو إذا تتذكرون ☺



The cascade is the oxidation cascade, and Primaquine will enhance this cascade which has benefits (to kill the parasites) and harmful effects (side effects, like damaging of RBCs)

WHO treatment guidelines

In vivax:

	Sensitive	Resistant
In vivax	Chloroquine for 3 days followed by Primaquine for 14 days Chloroquine to stop the symptoms and Primaquine to prevent relapse	ACT / 3 days followed by Primaquine for 14 days

In falicparum:

	uncomplicated	complicated
In falicparum (All show Resistance)	ACT (Artemisin-based Combination Therapies)	IV Artesunate for 24 hrs followed by ACT Or Artemether + [Clindamycin / doxycyline] They can treat any infection including parasite Or Quinine + [Clindamycin / Doxycyline]

Special risk group :

هذي النقطة مهمه

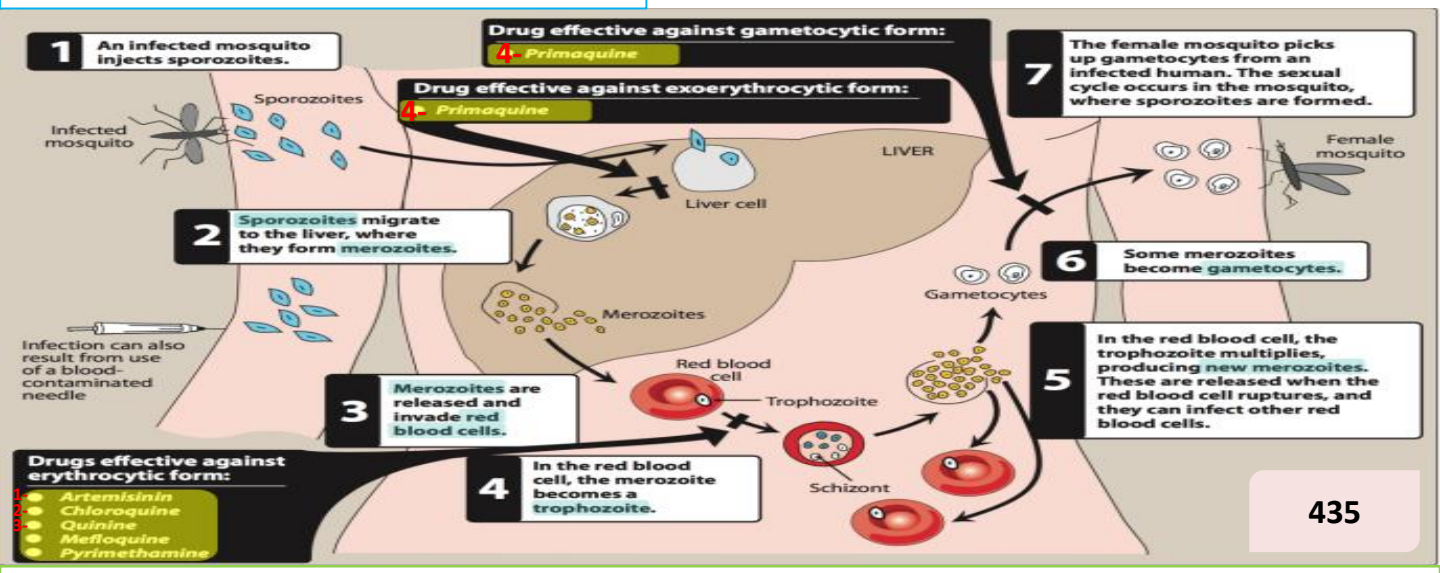
Quinine + Clindamycin (7 days):	ACT (Artemisin-based Combination Therapies):
Pregnancy; 1st trimester	■ Pregnancy; 2nd & 3rd trimester ■ Lactating women ■ So pregnant and lactating ladys use ACT, but after lactating she use Primaquine to eradicate the parasite in the liver (dose: 15 mg\day for 14 days) ■ Infants & young children

Prophylaxis in travelers

CDC (Control Disease Center) recommendations نشيك في موقعهم على توصياتهم قبل ما نسافر		
Chloroquine	Areas without resistant *P falciparum*	Begin 1-2 weeks before departure (except for doxycycline 2 days) & continue for 4 weeks after leaving the endemic area
Mefloquine	Areas with chloroquine-resistant *P falciparum*	
Doxycycline	Areas with multidrug-resistant *P falciparum*	

Summary

Life cycle of the malarial parasite & drugs site of action:



1-Artemisinin: **Fast** acting blood Schizontocide , **affect** all forms including multi-drug resistant *P. falciparum,* **short** duration of action, and **high** recrudescence rate after short-course therapy.

Clinical uses : Because artemisinin derivatives have short t½ :

Monotherapy should be extended beyond disappearance of parasite to prevent recrudescence or by **combining** the drug with long- acting antimalarial drugs (Ex. mefloquine) .

2-Chloroquine: **Potent** blood Schizontocidal, **active** against all forms of the schizonts (except chloroquine -resistant P.f. & P.v.), and a **gametoside**: Against all species except P. falciparum .

Clinical uses : Eradicate blood schizonts of Plasmodium, **Hepatic amoebiasis**, and **Rheumatoid arthritis** (it acts as anti-inflammatory drug).

3-Quinine: **It is quinidine** (anti-arrhythmic drug) isomer, both extracted from cinchona bark so it has some side effects of quinidine as depression of myocardium, reduce excitability & conductivity.**Potent** blood Schizontocide of ALL malarial parasites & **gametoside** for P vivax & ovale but not falciparum, **it is not active** against liver stage parasites, and **has other effects** like: Mild analgesic, antipyretic, stimulation of uterine smooth muscle (mild), curaremimetic effect (neuromuscular blocking effect).

Clinical uses : I.V (parenteral) treatment of severe falciparum malaria, **Oral** treatment of falciparum malaria, and **Nocturnal leg cramps**.

4-Primaquine: **Hypnozoitocides** against liver hypnozoites & gametocytocides against the 4 human malaria species, **radical cure** of P. ovale & P. vivax, and **Prevent** spread of ALL forms (chemoprophylaxis) .

Clinical uses : Radical cure of relapsing malaria 15 mg/day for 14 days, **In falciparum malaria:** a single dose (45 mg) to kill gametes & cut down transmission, and **Should be avoided in pregnancy** (the fetus is relatively G6PD-deficient & thus at risk of hemolysis) & **G6PD deficiency patients**.

Special Risk Groups: (WHO treatment guidelines In falciparum)

Quinine + Clindamycin (7 days) : pregnancy 1st trimester .

ACT : Pregnancy 2nd, 3rd trimesters, lactating women, infants, and young children.

Prophylaxis in travellers: (CDC recommendations)

Chloroquine : Areas without resistant P. Falciparum .

Mefloquine : Areas with chloroquine-resistant P. Falciparum.

Doxycycline : Areas with multidrug-resistant P. Falciparum.

Begin 1-2 weeks before departure (except doxycycline 2 days prior) & continue for 4 weeks after leaving endemic area .

MCQs

Q1: A group of college students are traveling to a chloroquine-resistant malaria area for a mission trip. Which of the following medications can be used for prevention of malaria in these students?

A. Pyrimethamine. B. Mefloquine. C. Primaquinine

Q2: Which one of the following antimalarial drugs act on liver mainly ?

A. Artemisinin. *B.* Pyrimethamine. *C.* Primaquine.

Q3: Which one of the following antimalarial drugs can be used in case of severe complicated cases of malaria such as cerebral malaria?

A. Artemisinin. B. Artesunate . C. Artemether.

Q4: Which one of the following antimalarial drugs act as heme polymerase inhibitors?

A. Artemisinin. *B.* Chloroquine. *C.* Primaquine.

Q5: Malaria can develop resistance against Chloroquine by which transporters ?

A. plasmodium o falciparum chloroquine resistance transporter .
B. P-glycoprotein transporter .
C. Both of them .

Q6: Malaria can develop resistance against Quinine by which transporters ?

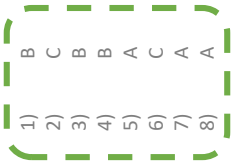
A. plasmodium o falciparum chloroquine resistance transporter .
B. P-glycoprotein transporter .
C. Both of them .

Q7: Which one of the following antimalarial drugs can cause Blackwater fever as serious adverse effect ?

A. Quinine. B. Chloroquine. C. Primaquine.

Q8: Patient with bradycardia and Arrhythmia, and his ECG shows prolong QT intervals. Which one of following antimalarial drug should be avoided in his case ?

A. Quinine. B. Chloroquine. C. Primaquine.



MCQs

Q9: Hemolytic anemia is a main side effect of :

A. Quinine. B. Chloroquine. C. Primaquine.

Q10: African child with G6PD deficiency who has infected by malaria which is resistant for chloroquine and artemether Which one of the following doses is required to eradicate them by primaquine ?

A. 15 mg\day for 14 days. B. 30 mg\week for 30 weeks. C. 45 mg\week for 8 weeks.

Q11: Turkish child with sever G6PD deficiency who has infected by malaria which is resistant for chloroquine and artemether Which one of the following doses is required to eradicate them by primaquine ?

A. 15 mg\day for 14 days. B. 30 mg\week for 30 weeks. C. 45 mg\week for 8 weeks.

Q12: which one of the following is the recommended dose of primaquine to be used in normal person without G6PD deficiency ?

A. 15 mg\day for 14 days. B. 30 mg\week for 30 weeks. C. 45 mg\week for 8 weeks.

Q13: A lady in her 2nd month of pregnancy. She get infected by malaria. Which one of the following Antimalarial drugs can be used in her case* ?

A. Artemether + mefloquine. B. Chloroquine. C. Primaquine.

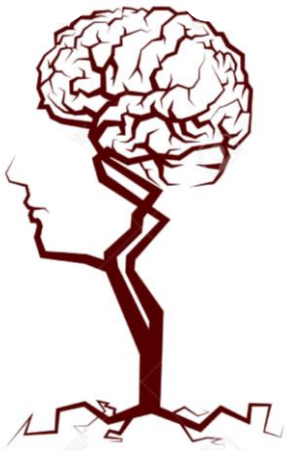
Q14: A lady in her 6th month of pregnancy. She get infected by malaria. Which one of the following Antimalarial drugs can be used in her case ?**

A. Artemether + mefloquine. B. Chloroquine. C. Primaquine.

9) C
10) C
11) B
12) A
13) B
14) A

***Both** Artemisinin & Primaquine **should be avoided in her case.**
Primaquine can not be used in all trimesters of pregnancy while Artemisinin and its derivatives can not be used in 1st trimesters only

**Pregnancy; 2nd & 3rd trimester & Lactating women & Infants & young children , the best for them is ACT.
But after lactating she has to use Primaquine to eradicate the parasite in the liver (dose: 15 mg\day for 14 days)



إِنَّ فِي ذَٰلِكَ لَآيَاتٍ لِّقَوْمٍ يَتَفَكَّرُونَ ﴿٣﴾

قادة فريق علم الأدوية :

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- فارس النفيسة

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شوق الأحمري
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خالد العيسى
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2- 435 pharmacology teamwork
3- 435 and 436 biochemistry teamwork

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* الشعار و القالب الأساسي من تصميم لين التميمي